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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/773,387	02/05/2004	David A. Estell	GC381-US-D2	7258

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EXAMINER	
STEADMAN, DAVID J	

ART UNIT	PAPER NUMBER
1656	

DATE MAILED: 10/04/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/773,387	ESTELL, DAVID A.	
	Examiner	Art Unit	
	David J. Steadman	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 July 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-35* is/are pending in the application.

4a) Of the above claim(s) *31-35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 February 2004* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/462,846.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/5/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Appendices A and B*.

DETAILED ACTION

Status of the Application

[1] Claims 23-35 are pending in the application.

[2] Applicant's preliminary amendment to the claims, filed 10 July 2006, is acknowledged. This listing of the claims replaces all prior versions and listings of the claims.

[3] Applicant's preliminary amendment to the specification, filed 10 July 2006, is acknowledged.

Election/Restriction

[4] Applicant's election without traverse of Group I, claims 23-30, in the reply filed 10 July 2006, is acknowledged.

[5] Claims 31-35 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 10 July 2006.

[6] Applicant's request to consider rejoinder of method claims 31-35 with product claims 23-30 is acknowledged. However, as no product claims are in condition for allowance, the examiner is not required to consider rejoinder of method claims with product claims at this time.

[7] Claims 23-30 are being examined on the merits.

Priority

[8] Applicant's claim to domestic priority under 35 USC § 120 to US Application No. 09/462,846, filed on 13 January 2000, now US Patent 6,762,039, is acknowledged. Application 09/462,846 is a filing under 35 U.S.C. 371 of international application PCT/US98/14529, filed 14 July 1998. Applicant's claim to foreign priority under 35 USC § 119(a)-(d) to EPO application 97305227.7, filed 15 July 1997, is acknowledged. A certified copy of the foreign priority document was filed in parent application 09/462,846 on 13 January 2000.

Oath/Declaration

[9] It is noted that applicant has changed the relationship of the instant application to the prior filed application to being a continuation-in-part. It is noted that a copy of the declaration from parent application 09/462,846 has been filed on 5 February 2004. However, in accordance with 37 CFR 1.63(e), which states, "[a] newly executed oath or declaration must be filed in any continuation-in-part application, which application may name all, more, or fewer than all of the inventors named in the prior application," a newly executed oath or declaration is required.

Information Disclosure Statement

[10] With the exception of references Ausubel et al., Berger and Kimmel, Coombs, Dieffenbach et al., Glover, Hampton et al., Harwood et al. (1990), Harwood et al. (1989), Sambrook et al., and Webb Academic Press, all references cited in the IDS filed on 5 February 2004 have been considered by the examiner. A copy of Forms PTO-1449 is

attached to the instant Office action. The references noted above have not been considered as a copy of each of the references has not been filed in the instant application or parent application 09/462,286 as required by 37 CFR 1.98(a)(2).

Drawings

[11] The drawings are objected to as disclosing sequences that have not been properly identified by a sequence identifier. When a sequence is presented in a drawing, regardless of the format or the manner of presentation of that sequence in the drawing, the sequence must still be included in the Sequence Listing and the sequence identifier ("SEQ ID NO:X") must be used, either in the drawing or in the Brief Description of the Drawings. See MPEP § 2422.02.

Claim Objections

[12] Claims 23 and 26 are objected to in the recitation of "CP3" in claim 23 and "Apr," "Npr," "Epr," "Wpr," and "Mpr" in claim 26. Abbreviations, unless otherwise obvious and/or commonly used in the art, *e.g.,* DNA, should not be recited in the claims without at least once reciting the entire phrase for which the abbreviation is used. Appropriate correction is required.

[13] Claim 30 is objected to as being grammatically incorrect in the recitation of "group consisting of a proteases" and it is suggested that "a" in the phrase "group consisting of a proteases" be deleted.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

[14] Claims 23-30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

[a] Claim 23 (claims 24-25 and 27-30 dependent therefrom) and 26 are indefinite in the recitation of "CP3" in claim 23 and "Apr," "Npr," "Epr," "Wpr," and "Mpr" in claim 26. Neither the specification nor the claims set(s) forth a definition of the terms "CP3," "Apr," "Npr," "Epr," "Wpr," and/or "Mpr and there does not appear to be an art-recognized meaning of the terms "CP3," "Apr," "Npr," "Epr," "Wpr," and "Mpr" such that a skilled artisan would be able to determine the intended scope of polypeptides that are encompassed by the terms. In the interest of advancing prosecution, the examiner has interpreted the term "CP3" as encompassing any polypeptide – excluding SEQ ID NO:2 and 6 – having cysteine protease activity and has interpreted the terms "Apr," "Npr," "Epr," "Wpr," and "Mpr" as polypeptides having any protease activity. It is suggested that applicant clarify the meanings of the terms "CP3," "Apr," "Npr," "Epr," "Wpr," and "Mpr."

[b] Claim 23 (claims 24-30 dependent therefrom) recites the limitation "the gene encoding CP3." There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

[15] Claims 23-30 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or well-established utility. The claims are drawn to a gram-positive microorganism having a mutation or deletion in all or part of the gene encoding CP3, wherein the mutation or deletion results in the inactivation of the CP3 proteolytic activity.

The specification discloses CP3 is a *B. subtilis* cysteine protease, the function of which appears to have been assigned based upon "the presence of the characteristic cysteine protease amino acid motif GXCWAF found in uncharacterised translated genomic nucleic acid sequences of Bacillus subtilis" and "the structural relatedness that CP1 has with the cysteine protease papain specifically with respect to the location of the catalytic histidine/alanine and asparagine/serine residues and the structural relatedness that CP1 has with CP2 and CP3" (specification at p. 2, lines 11-17). The function of CP3 appears to be based solely on structural characteristics of the primary amino acid sequence of SEQ ID NO:5. The specification asserts the use of the invention as a host for recombinant protein expression with diminished or deleted CP3 activity (specification at p. 15, lines 14-17).

An analysis of the sequence of CP3 sequence of SEQ ID NO:5 reveals that the "characteristic cysteine protease amino acid motif GXCWAF" appears to be absent in SEQ ID NO:5 and there is no evidence of record that the polypeptide of SEQ ID NO:5

has cysteine protease activity. Further, it is noted that a prior art search of the sequence of SEQ ID NO:4 reveals a 100% identity match with a polypeptide referred to as a phosphomannose isomerase, independently isolated and annotated by two different groups (see Rashid et al. *Microbiol* 141:2391-2404, 1995, which refers to the phosphomannose isomerase as "pmi" and Margot et al. *Mol Microbiol* 12:535-545, 1994, which refers to the phosphomannose isomerase as "OrfX," and which is cited in the IDS filed on 5 February 2004). See Appendices A and B. Margot et al. teaches "[a]nalyses of deduced amino acid sequences revealed a significant homology (Fig. 3) between OrfX and both the *Escherichia coli* and *Salmonella typhimurium* 6-phosphate phosphomannose isomerase" (p. 536, right column, bottom). Rashid et al. is in agreement with the findings of Margot et al. in stating "[a] computer search revealed significant amino acid sequence similarity between the Pmi, and the *E. coli manA*...and *Salmonella typhimurium pmi* gene products" (p. 2397, left column, top). As such, there is reasonable support for a conclusion that CP3 of SEQ ID NO:5 may not be a cysteine protease, but a phosphomannose isomerase. At least for the reasons stated above, it would appear that further experimentation is required to identify a "real-world" use for the claimed invention. This type of utility is not substantial as the specification must teach a skilled artisan how to use what is claimed and not merely provide a blueprint for further experimentation in order for an artisan to identify a use for the claimed invention. See Brenner v. Manson, 383 U.S. 519, 148 USPQ 689 (Sup. Ct. 1966). As stated in Brenner v. Manson, 383 U.S. 519 535-536, 148 USPQ 689, 696 (1966), "[a] patent is not a hunting license. It is not a reward for the search, but compensation for its

successful conclusion." Thus, the claimed invention is not supported by a specific and substantial asserted utility.

[16] Claims 23-30 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

[17] Claims 23-30 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claim 23 (claims 24-30 dependent therefrom) is drawn to a gram-positive microorganism having a mutation or deletion in all or part of the gene encoding CP3, wherein the mutation or deletion results in the inactivation of the CP3 proteolytic activity. According to MPEP § 2163.I., "[t]o satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in

the art can reasonably conclude that the inventor had possession of the claimed invention." In this case, the invention is a host cell with inactivated CP3 proteolytic activity. However, as noted above, the prior art recognizes the sequence of CP3 as being the sequence of a phosphomannose isomerase polypeptide – not a polypeptide with cysteine protease activity. As such, a skilled artisan cannot "reasonably conclude that the inventor had possession of the claimed invention."

Also, claims 23 (claims 24-25 and 27-30 dependent therefrom) and 26 are drawn to a genus of host cells having mutation or deletion in all or part of a genus of "CP3," "Apr," "Npr," "Epr," "Wpr," and "Mpr" genes. For claims drawn to a genus, MPEP § 2163 states the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus. In this case, the specification discloses only a single representative species of the recited genus of host cells, *i.e.*, a *Bacillus subtilis* having a deletion of SEQ ID NO:4. The specification fails to describe any additional representative species of the recited genus

of host cells. While MPEP § 2163 acknowledges that in certain situations "one species adequately supports a genus," it also acknowledges that "[f]or inventions in an unpredictable art, adequate written description of a genus which embraces widely variant species cannot be achieved by disclosing only one species within the genus." In the instant case, the recited genus of host cells encompasses species that are widely variant. As such, the disclosure of the single representative species as noted above is insufficient to be representative of the attributes and features of all species of host cells, particularly with respect to the genus of CP3 genes encompassed by the claims. Also, regarding the genus of host cells having a mutation or deletion in one or more of "Apr," "Npr," "Epr," "Wpr," and "Mpr" genes, the specification fails to disclose the structure of even a single representative species of "Apr," "Npr," "Epr," "Wpr," and "Mpr" genes and further fails to disclose even a single representative species of host cells with a mutation or deletion of "Apr," "Npr," "Epr," "Wpr," and "Mpr" genes as encompassed by the claims. In this case, the recitation of "CP3," "Apr," "Npr," "Epr," "Wpr," and "Mpr" fails to provide a sufficient description of the recited genus of genes as it merely describes the functional features of the genus without providing any definition of the structural features of the species within the genus. The CAFC in *Regents of the University of California v. Eli Lilly*, (43 USPQ2d 1398) stated that: "[i]n claims to genetic material, however a generic statement such as 'vertebrate insulin cDNA' or 'mammalian insulin cDNA,' without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural

features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus." Similarly with the recited genus of genes, the functional definition of the genus does not provide any structural information commonly possessed by members of the genus which distinguish the nucleic acid species within the genus from others such that one can visualize or recognize the identity of the members of the genus.

Given the lack of description of a representative number of polypeptides, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicant was in possession of the claimed invention.

[18] Even if there is a "real world" utility for the claimed invention, the following rejection still applies. Claims 23-30 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a *Bacillus subtilis* having a chromosomal mutation or deletion of part or all of the CP3 gene of SEQ ID NO:4, wherein said mutation or deletion results in the inactivation of CP3 cysteine protease activity, does not reasonably provide enablement for all host cells having any mutation or deletion of any gene considered to be a "CP3" gene to reduce CP3 proteolytic activity, optionally further having any mutation or deletion of "Apr," "Npr," "Epr," "Wpr," and "Mpr" genes as broadly encompassed by the claims. The specification does not

enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

It is the examiner's position that undue experimentation is required for a skilled artisan to make and/or use the entire scope of the claimed invention. Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)) as follows: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure. See MPEP § 2164.01(a). MPEP 2164.04 states, "[w]hile the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection" and that "[t]he language should focus on those factors, reasons, and evidence that lead the examiner to conclude that the specification fails to teach how to make and use the claimed invention without undue experimentation, or that the scope of any enablement provided to one skilled in the art is not commensurate with the scope of protection sought by the claims." Accordingly, the Factors most relevant to the instant rejection are addressed in detail below.

The breadth of the claims: As noted above, the examiner has interpreted the term "CP3" as encompassing any polypeptide – excluding SEQ ID NO:2 and 6 – having cysteine protease activity and has interpreted the terms "Apr," "Npr," "Epr," "Wpr," and "Mpr" as

polypeptides having any protease activity. Thus, the claims are so broad as to encompass any gram-positive microorganism having a mutation or deletion in part or all of any gene considered to be a "CP3" gene that results in inactivation of "CP3" proteolytic activity, optionally wherein the host cell has a mutation or deletion of any genes considered to be "Apr," "Npr," "Epr," "Wpr," and "Mpr" genes as broadly encompassed by the claims. The enablement provided by the specification is not commensurate in scope with the claims with regard to the number of host cells and mutated or deleted genes encompassed by the claims. In this case, the specification is enabling only for a *Bacillus subtilis* having a chromosomal mutation or deletion of part or all of the CP3 gene of SEQ ID NO:4, wherein said mutation or deletion results in the inactivation of CP3 proteolytic activity.

The state of the prior art; The level of one of ordinary skill; and The level of predictability in the art: The nucleotide sequence encoding a polypeptide determines the polypeptide's structural and functional properties. Predictability of which changes can be made in a protein's amino acid sequence and obtain the desired activity/utility requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant or intolerant to modification and detailed knowledge of the ways in which the protein's structure relates to its function. The positions within a protein's sequence where modifications can be made with a reasonable expectation of success in obtaining a polypeptide having a desired activity/utility are limited in any protein and the result of such modification(s) is highly unpredictable. See, for example, Branden et al. ("Introduction to Protein Structure", Garland Publishing Inc., New York, 1991, p. 247)

and Witkowski et al. (Biochemistry 38:11643-11650, 1999). At the time of the invention, methods for specifically inactivating a gene were known in the art, *e.g.*, homologous recombination. However, neither the specification nor the state of the art at the time of the invention provided the necessary guidance for altering the nucleic acid of SEQ ID NO:4 or the polypeptide of SEQ ID NO:5 with an expectation of obtaining a polypeptide having inactivated CP3 activity.

The amount of direction provided by the inventor and The existence of working examples: In this case, the specification discloses only a single working example of the claimed microorganism, *i.e., a Bacillus subtilis* having a chromosomal inactivation of SEQ ID NO:4 due to homologous recombination, wherein said inactivation results in the inactivation of CP3 cysteine protease activity. The specification fails to disclose any specific guidance for mutating the CP3 gene of SEQ ID NO:4 with an expectation that the resulting variants of SEQ ID NO:4 as encompassed by the claims will achieve the desired activity/utility of inactivated CP3 cysteine protease activity.

The quantity of experimentation needed to make or use the invention based on the content of the disclosure: While methods of isolating and/or generating variants of a gene were known in the art at the time of the invention, it was not routine in the art to screen – by a trial and error process – for all microorganisms having a substantial number of modifications as encompassed by the claims for those that have inactivated CP3 activity.

In view of the overly broad scope of the claims, the lack of guidance and working examples provided in the specification, the high level of unpredictability as evidenced by the prior art, and the amount of experimentation required, undue experimentation is necessary for a skilled artisan to make and use the entire scope of the claimed invention. Applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

[19] Claims 23-30 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 89/10976 (cited in the IDS filed 5 February 2006). The claims are drawn to a gram-positive microorganism having a mutation or deletion in all or part of the gene encoding CP3, wherein the mutation or deletion results in the inactivation of the CP3 proteolytic

activity. The terms "CP3," "Apr," "Npr," "Epr," "Wpr," and "Mpr" have been interpreted in accordance with MPEP 2111 as noted above.

The reference of WO 89/10976 discloses the inactivation of genes encoding *B. subtilis* cysteine and serine proteases in a neutral and alkaline protease-deficient *B. subtilis* host cell (abstract and pp. 3-4 and 15-16) to create a mutant *B. subtilis* strain that is deficient in all four protease activities (pp. 15-16). WO 89/10976 teaches the use of the mutant strain for heterologous expression of prolysostaphin and lysostaphin, a metallopeptidase (pp. 11-12 and 16-17). This anticipates claims 23-30 as written.

Specification/Informalities

[20] According to the specification, "[t]he present invention relates to...three heretofore unknown or unrecognized cysteine proteases found in Bacillus subtilis, designated herein as CP1, CP2 and CP3 having the nucleic acid and amino acid as shown in FIGS. 1A-1B, FIGS. 5A-5B and 6A-6B, respectively" (specification at p. 2, lines 8-11). The specification is objected to as being confusing as the nucleic acid of SEQ ID NO:4 and the polypeptide of SEQ ID NO:5 as set forth in Figures 6A and 6B are recognized in the prior art as being a phosphomannose isomerase nucleic acid and polypeptide, respectively. It is suggested that applicant clarify this discrepancy in the application.

[21] This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37

CFR 1.821 through 1.825; applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). To be in compliance, applicants should identify nucleotide sequences of at least 10 nucleotides and amino acid sequences of at least 4 amino acids in the specification by a proper sequence identifier, i.e., "SEQ ID NO:" (see MPEP 2422.01). If these sequences have not been listed in the computer readable form and paper copy of the sequence listing, applicant must provide an initial computer readable form (CRF) copy of the "Sequence Listing", an initial paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification, and a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. 1.821(e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d). See particularly p. 2, line 13; p. 4, line 6; and p. 16, line 35.

Conclusion

[22] Status of the claims:

- Claims 23-35 are pending.
- Claims 31-35 are withdrawn from consideration.
- Claims 23-30 are rejected.
- No claim is in condition for allowance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Steadman whose telephone number is 571-272-0942. The examiner can normally be reached on Mon to Fri, 7:30 am to 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

David J. Steadman, Ph.D.
Primary Examiner
Art Unit 1656

APPENDIX A

A69680
mannose-6-phosphate isomerase (EC 5.3.1.8) pmi - Bacillus subtilis
C;Species: Bacillus subtilis
C;Date: 05-Dec-1997 #sequence_revision 05-Dec-1997 #text_change 09-Jul-2004
C;Accession: A69680; S49389
R;Kunst, F.; Ogasawara, N.; Moszer, I.; Albertini, A.M.; Alloni, G.; Azevedo, V.; Bertero, M.G.; Bessieres, P.; Bolotin, A.; Borchert, S.; Boriss, R.; Boursier, L.; Brans, A.; Braun, M.; Brignell, S.C.; Bron, S.; Brouillet, S.; Bruschi, C.V.; Caldwell, B.; Capuano, V.; Carter, N.M.; Choi, S.K.; Codani, J.J.; Connerton, I.F.; Cummings, N.J.; Daniel, R.A.; Denizot, F.; Devine, K.M.; Duesterhoeft, A.; Ehrlich, S.D.; Emmerson, P.T.; Entian, K.D.; Errington, J.; Fabret, C.; Ferrari, E.
Nature 390, 249-256, 1997
A;Authors: Foulger, D.; Fritz, C.; Fujita, M.; Fujita, Y.; Fuma, S.; Galizzi, A.; Galleron, N.; Ghim, S.Y.; Glaser, P.; Goffeau, A.; Golightly, E.J.; Grandi, G.; Guiseppi, G.; Guy, B.J.; Haga, K.; Haiech, J.; Harwood, C.R.; Henaut, A.; Hilbert, H.; Holsappel, S.; Hosono, S.; Hullo, M.F.; Itaya, M.; Jones, L.; Joris, B.; Karamata, D.; Kasahara, Y.; Klaerr-Blanchard, M.; Klein, C.; Kobayashi, Y.; Koetter, P.; Koningstein, G.; Krogh, S.; Kumano, M.; Kurita, K.; Lapidus, A.; Lardinois, S.
A;Authors: Lauber, J.; Lazarevic, V.; Lee, S.M.; Levine, A.; Liu, H.; Masuda, S.; Mauel, C.; Medigue, C.; Medina, N.; Mellado, R.P.; Mizuno, M.; Moestl, D.; Nakai, S.; Noback, M.; Noone, D.; O'Reilly, M.; Ogawa, K.; Ogiwara, A.; Oudega, B.; Park, S.H.; Parro, V.; Pohl, T.M.; Portetelle, D.; Porwolik, S.; Prescott, A.M.; Presecan, E.; Pujic, P.; Purnelle, B.; Rapoport, G.; Rey, M.; Reynolds, S.; Rieger, M.; Rivolta, C.; Rocha, E.; Roche, B.; Rose, M.; Sadaie, Y.; Sato, T.; Scanlon, E.
A;Authors: Schleich, S.; Schroeter, R.; Scoffone, F.; Sekiguchi, J.; Sekowska, A.; Seror, S.J.; Serror, P.; Shin, B.S.; Soldo, B.; Sorokin, A.; Tacconi, E.; Takagi, T.; Takahashi, H.; Takemaru, K.; Takeuchi, M.; Tamakoshi, A.; Tanaka, T.; Terpstra, P.; Tognoni, A.; Tosato, V.; Uchiyama, S.; Vandenbol, M.; Vannier, F.; Vassarotti, A.; Viari, A.; Wambutt, R.; Wedler, E.; Wedler, H.; Weitzenegger, T.; Winters, P.; Wipat, A.; Yamamoto, H.; Yamane, K.; Yasumoto, K.; Yata, K.; Yoshida, K.
A;Authors: Yoshikawa, H.F.; Zumstein, E.; Yoshikawa, H.; Danchin, A.
A;Title: The complete genome sequence of the Gram-positive bacterium Bacillus subtilis.
A;Reference number: A69580; MUID:98044033; PMID:9384377
A;Accession: A69680
A;Status: preliminary; nucleic acid sequence not shown; translation not shown
A;Molecule type: DNA
A;Residues: 1-316
A;Cross-references: UNIPROT:P39841; UNIPARC:UPI0000031A3A; GB:Z99122; GB:AL009126; NID:g2636029; PIDN:CAB15596.1; PID:e1184485; PID:g2636105
A;Experimental source: strain 168
R;Margot, P.; Mauel, C.; Karamata, D.
Mol. Microbiol. 12, 535-545, 1994
A;Title: The gene of the N-acetylglucosaminidase, a Bacillus subtilis 168 cell wall hydrolase not involved in vegetative cell autolysis.
A;Reference number: S49389; MUID:95020588; PMID:7934877
A;Accession: S49389
A;Status: preliminary; nucleic acid sequence not shown
A;Molecule type: DNA
A;Residues: 1-316
A;Cross-references: UNIPARC:UPI0000031A3A; EMBL:U02562; NID:g476091; PIDN:AAA67856.1; PID:g476092
C;Genetics:
A;Gene: pmi
C;Keywords: intramolecular oxidoreductase; isomerase

Alignment Scores:

Pred. No.:	6.6e-138	Length:	316
Score:	1698.00	Matches:	316
Percent Similarity:	100.0%	Conservative:	0
Best Local Similarity:	100.0%	Mismatches:	0
Query Match:	100.0%	Indels:	0
DB:	2	Gaps:	0

US-10-773-387-4 (1-948) x A69680 (1-316)

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Qy          1 ATGACGCAATCACCGATTTTTCTAACGCCTGTGTTTAAAGAAAAAATCTGGGGCGGAACC 60
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db          1 MetThrGlnSerProIlePheLeuThrProValPheLysGluLysIleTrpGlyGlyThr 20

Qy         61 GCTTTACGAGATAGATTTGGATACAGTATTCCTTCAGAATCAACGGGGGAATGCTGGGCC 120
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         21 AlaLeuArgAspArgPheGlyTyrSerIleProSerGluSerThrGlyGluCysTrpAla 40

Qy        121 ATTTCCGCTCATCCAAAAGGACCGAGCACTGTTGCAAATGGCCCGTATAAAGGAAAGACA 180
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         41 IleSerAlaHisProLysGlyProSerThrValAlaAsnGlyProTyrLysGlyLysThr 60

Qy        181 TTGATCGAGCTTTGGGAAGAGCACCGTGAAGTATTCGGCGGCGTAGAGGGGGATCGGTTT 240
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         61 LeuIleGluLeuTrpGluGluHisArgGluValPheGlyGlyValGluGlyAspArgPhe 80

Qy        241 CCGCTTCTGACAAAGCTGCTGGATGTGAAGGAAGATACGTCAATTAAAGTTCACCCTGAT 300
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db         81 ProLeuLeuThrLysLeuLeuAspValLysGluAspThrSerIleLysValHisProAsp 100

Qy        301 GATTACTATGCCGGAGAAAACGAAGAGGGAGAACTCGGCAAGACGGAATGCTGGTACATT 360
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        101 AspTyrTyrAlaGlyGluAsnGluGluGlyGluLeuGlyLysThrGluCysTrpTyrIle 120

Qy        361 ATCGACTGTAAGGAAAACGCAGAAATCATTTACGGGCATACGGCCCGCTCAAAAACCGAA 420
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        121 IleAspCysLysGluAsnAlaGluIleIleTyrGlyHisThrAlaArgSerLysThrGlu 140

Qy        421 CTTGTCACAATGATCAACAGCGGTGACTGGGAGGGCCTGCTGCGAAGAATCAAAATTAAA 480
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
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Db        141 LeuValThrMetIleAsnSerGlyAspTrpGluGlyLeuLeuArgArgIleLysIleLys 160

Qy        481 CCGGGTGATTTCTATTATGTGCCGAGCGGAACGCTGCACGCATTGTGCAAGGGGGCCCTT 540
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        161 ProGlyAspPheTyrTyrValProSerGlyThrLeuHisAlaLeuCysLysGlyAlaLeu 180

Qy        541 GTTTTAGAGACTCAGCAAAATTCAGATGCCACATACCGGGTGTACGATTATGACCGTCTT 600
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        181 ValLeuGluThrGlnGlnAsnSerAspAlaThrTyrArgValTyrAspTyrAspArgLeu 200

Qy        601 GATAGCAACGGAAGTCCGAGAGAGCTTCATTTTGCCAAAGCGGTCAATGCCGCCACGGTT 660
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        201 AspSerAsnGlySerProArgGluLeuHisPheAlaLysAlaValAsnAlaAlaThrVal 220

Qy        661 CCCCATGTGGACGGGTATATAGATGAATCGACAGAATCAAGAAAAGGAATAACCATTAAA 720
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        221 ProHisValAspGlyTyrIleAspGluSerThrGluSerArgLysGlyIleThrIleLys 240

Qy        721 ACATTTGTCCAAGGGGAATATTTTTCGGTTTATAAATGGGACATCAATGGCGAAGCTGAA 780
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        241 ThrPheValGlnGlyGluTyrPheSerValTyrLysTrpAspIleAsnGlyGluAlaGlu 260

Qy        781 ATGGCTCAGGATGAATCCTTTCTGATTTGCAGCGTGATAGAAGGAAGCGGTTTGCTCAAG 840
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        261 MetAlaGlnAspGluSerPheLeuIleCysSerValIleGluGlySerGlyLeuLeuLys 280

Qy        841 TATGAGGACAAAACATGTCCGCTCAAAAAAGGTGATCACTTTATTTTGCCGGCTCAAATG 900
              ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db        281 TyrGluAspLysThrCysProLeuLysLysGlyAspHisPheIleLeuProAlaGlnMet 300

Qy        901 CCCGATTTTACGATAAAAGGAACTTGTACCCTTATCGTGTCTCATATT 948
              ||||||||||||||||||||||||||||||||||||||||||||||||
Db        301 ProAspPheThrIleLysGlyThrCysThrLeuIleValSerHisIle 316
```

APPENDIX B

Query sequence 1

```
>SEQ ID NO:5
MTQSPIFLTPVFKEKIWGGTALRDRFGYSIPSESTGECWAISAHPKGPSTVANGPYKGKT
LIELWEEHREVFGGVEGDRFPLLTKLLDVKEDTSIKVHPDDYYAGENEEGELGKTECWYI
IDCKENAEIIYGHTARSKTELVTMINSGDWEGLLRRIKIKPGDFYYVPSGTLHALCKGAL
VLETQQNSDATYRVYDYDRLDSNGSPRELHFAKAVNAATVPHVDGYIDESTESRKGITIK
TFVQGEYFSVYKWDINGEAEMAQDESFLICSVIEGSGLLKYEDKTCPLKKGDHFILPAQM
PDFTIKGTCTLIVSHI
```

Query sequence 2

```
>gi|732325|sp|P39841|MANA_BACSU Mannose-6-phosphate isomerase (Phosphomannose isomerase) (PMI) (Phosphohexomutase)
MTQSPIFLTPVFKEKIWGGTALRDRFGYSIPSESTGECWAISAHPKGPSTVANGPYKGKT
LIELWEEHREVFGGVEGDRFPLLTKLLDVKEDTSIKVHPDDYYAGENEEGELGKTECWYI
IDCKENAEIIYGHTARSKTELVTMINSGDWEGLLRRIKIKPGDFYYVPSGTLHALCKGAL
VLETQQNSDATYRVYDYDRLDSNGSPRELHFAKAVNAATVPHVDGYIDESTESRKGITIK
TFVQGEYFSVYKWDINGEAEMAQDESFLICSVIEGSGLLKYEDKTCPLKKGDHFILPAQM
PDFTIKGTCTLIVSHI
```

Full-length alignment between two sequences

```
>>gi|732325|sp|P39841|MANA_BACSU Mannose-6-phosphate iso  (316 aa)
 s-w opt: 2150  Z-score: 2639.5  bits: 496.6 E(): 3.2e-145
Smith-Waterman score: 2150;  100.000% identity (100.000% ungapped) in 316 aa overlap (1-316:1-316)

               10        20        30        40        50        60
SEQ     MTQSPIFLTPVFKEKIWGGTALRDRFGYSIPSESTGECWAISAHPKGPSTVANGPYKGKT
        ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
gi|732 MTQSPIFLTPVFKEKIWGGTALRDRFGYSIPSESTGECWAISAHPKGPSTVANGPYKGKT
               10        20        30        40        50        60

               70        80        90       100       110       120
SEQ     LIELWEEHREVFGGVEGDRFPLLTKLLDVKEDTSIKVHPDDYYAGENEEGELGKTECWYI
        ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
gi|732 LIELWEEHREVFGGVEGDRFPLLTKLLDVKEDTSIKVHPDDYYAGENEEGELGKTECWYI
               70        80        90       100       110       120

              130       140       150       160       170       180
SEQ     IDCKENAEIIYGHTARSKTELVTMINSGDWEGLLRRIKIKPGDFYYVPSGTLHALCKGAL
        ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
gi|732 IDCKENAEIIYGHTARSKTELVTMINSGDWEGLLRRIKIKPGDFYYVPSGTLHALCKGAL
              130       140       150       160       170       180

              190       200       210       220       230       240
SEQ     VLETQQNSDATYRVYDYDRLDSNGSPRELHFAKAVNAATVPHVDGYIDESTESRKGITIK
        ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
gi|732 VLETQQNSDATYRVYDYDRLDSNGSPRELHFAKAVNAATVPHVDGYIDESTESRKGITIK
              190       200       210       220       230       240

              250       260       270       280       290       300
SEQ     TFVQGEYFSVYKWDINGEAEMAQDESFLICSVIEGSGLLKYEDKTCPLKKGDHFILPAQM
        ::::::::::::::::::::::::::::::::::::::::::::::::::::::::::::
gi|732 TFVQGEYFSVYKWDINGEAEMAQDESFLICSVIEGSGLLKYEDKTCPLKKGDHFILPAQM
              250       260       270       280       290       300

              310
SEQ     PDFTIKGTCTLIVSHI
        ::::::::::::::::
gi|732 PDFTIKGTCTLIVSHI
              310
```